MEMORANDUM

***Subject*:** **Clinical Team Leader BLA review memo**
From: **Peter Bross, Clinical Oncology Team Leader, OCTGT/CBER**
***To*:** **STN 125197 Sipuleucel-T/Provenge® BLA file**
Through **Celia Witten, Office Director OCTGT/CBER**
Date: **May, 4, 2007**

Background: PROVENGE® (Sipuleucel T, APC8015) is an autologous cellular immunotherapy product consisting of peripheral blood mononuclear cells (PBMCs) obtained from patients by leukapheresis and activated *in vitro* with a recombinant fusion protein (prostatic acid phosphatase fused with GM-CSF). This cellular product is then re-infused intravenously into the patients, and is thought to activate T cells to create an immune response against the patients' prostate cancer. This product was studied in the treatment of men with asymptomatic metastatic androgen independent prostate cancer. The efficacy claim of this BLA submission is based on an observed survival difference by log rank test favoring the Sipuleucel T treatment seen in one completed phase 3 study of 127 patients. The primary efficacy endpoint was time to objective disease progression, defined as the time from randomization to the first observation of disease progression. This study failed to achieve its primary objective of an increase in time to progression, however, a survival difference of 4.5 months favoring the treatment arm was noted following 36 months follow up. Review of the submitted data including review of study conduct, baseline disease characteristics, therapeutic interventions, and statistical sensitivity analyses supported the findings of a survival difference in this study, however there was no evidence of an effect upon time to progression, tumor shrinkage, or delay in onset of disease related pain. The conservative statistical conclusion in this situation would be to assume that in the setting of a failed primary objective, any positive statistical findings are attributable to chance, however the novel mechanism of action and the clinically meaningful 4.5 month survival finding led to CBER filing and reviewing the BLA. Docetaxel, given every 3 weeks, has a 2.4 month median survival advantage over mitoxantrone and is the only therapy which has demonstrated a conclusive survival advantage in hormone refractory prostate cancer.

Study design: Two similarly designed, randomized, double-blind, placebo-controlled phase 3 trials, D9901 and D9902A, and evidence from additional non randomized studies are submitted in support of efficacy and safety in this BLA. The stated primary objective of D9901 and D9902A was to test whether the treatment with Sipuleucel T could increase the time to disease progression by 3.7 months in patients with asymptomatic metastatic AIPC compared with treatment by APC placebo. For details regarding the manufacture of these products, please see the CMC review by Dr Wonnacott. Disease progression was defined by objective radiographical criteria, clinical progression and pain progression criteria. Prostate-Specific Antigen (PSA) was measured, but not used as a criterion for disease progression. The trials were not powered to detect a survival difference and the primary method for survival analysis was not pre-defined, but survival data were collected as part of the safety evaluation. Major eligibility criteria included histologically documented adenocarcinoma of the prostate, >25% of tumor cells staining positive for PAP, asymptomatic metastatic disease either in the soft tissue or bone, and evidence of tumor progression after hormonal therapy either by radiographic or PSA criteria. Subjects were stratified by study center and bisphosphonate use, centrally randomized in a 2:1 ratio of APC 8015 to APC-Placebo, and scheduled to receive three intravenous infusions of either Sipuleucel T or APC-placebo preceded by leukapheresis 2 to 3 days prior to the infusion date on weeks 0, 2 and 4. Patients were evaluated

at weeks 2, 4, 12, and clinical evaluations were combined with radiographic tumor staging at baseline, weeks 8, 16, 24, and 32, and every 12 weeks thereafter until disease progression. Staging scans were reviewed by an independent radiology facility to confirm objective disease progression. Subjects were monitored for delayed treatment-related adverse events (AEs) and for survival for 36 months or until death. For details regarding the study design, please see Dr Ke Liu's clinical BLA review.

Study Results:

D9901: Study D9901 screened 186 patients to enroll 127 subjects. Eighty two were randomized to the Sipuleucel T arm and 45 to the APC-Placebo arm. Some imbalances were noted in the baseline demographic and prognostic characteristics including Gleason grading and disease location (bone, soft tissue or both) between the two arms. Sensitivity analyses did not suggest that these imbalances confounded the survival results. African-American and Hispanic subjects were underrepresented in this patient population.

Primary efficacy analysis of time to progression:

Progression events: Out of 127 subjects randomized, 114 developed disease progression. Ninety-eight subjects were documented to have disease progression based on the imaging studies. Ten subjects had clinical events of disease progression and 7 subjects developed new onset of disease pain correlated with imaging studies. There were 12 censored events (13.4%) for Sipuleucel T arm and 1 (2.2%) censored event for APC-placebo. Although the curves appeared to separate at week 10, there was no overall statistical difference between the two curves; Estimated median time to disease progression was 11.0 weeks (ranging from 2.1 weeks to 57.4) for Sipuleucel T and 9.1 weeks (ranging from 3.9 weeks to 52.1) for placebo. In the June 2002 analysis after unblinding of the locked database, the difference in the time to disease progression (TTP) seen between the two arms in the ITT population did not reach statistical significance ($p = 0.085$ by log-rank test). Subsequently, a complete clinical audit was performed to compare source documentation at the clinical study centers to the clinical database, resulting in the changes of progression dates in six subjects. Based upon this unblinded audit and revision of progression dates, the applicant re-analyzed the primary endpoint results and reported a p-value of 0.052 for the primary TTP endpoint difference. FDA's review of the revised progression dates from case report forms and sponsor's additional information showed that the changes in the progression dates from two subjects were primarily responsible for lowering p-value to 0.052. The FDA concluded that the sponsor's claimed p-value is derived from an analysis resulting from an unblinded study audit. This audit was not prespecified in the imaging charter or study protocol. The reduction in the p-value was primarily driven by the revision of progression dates or censoring from two subjects in a study with a small sample size. A review of case report forms revealed that the FDA disagreed with the sponsor with respect to 18 progression dates in the active arm and 7 progression dates in the placebo arm. In almost all of these cases the FDA judged that the progression event occurred earlier than the sponsor's estimate.

Since the BLA claim was based on a survival advantage in favor of Sipuleucel T treatment, not on the results of the primary endpoint, and there were so many uncertainties regarding the endpoint, FDA did not require a complete reassessment of the time to disease progression data. FDA considers a p-value of 0.085 by log-rank test to be the result from the primary analysis specified in the protocol, and the p-value of 0.052 by log-rank test to be derived from an exploratory analysis. Although the

BLA claim was based on survival, time to progression was important because it was the primary endpoint. The primary efficacy analysis of D9901 results showed that the study did not achieve its primary objective of prolonged time to objective disease progression or any other pre-specified efficacy endpoint. The failure of the study to achieve its primary objective makes it very difficult to determine if additional positive findings could be attributable to chance.

Survival analysis: A 3-year survival analysis of D9901 was performed as part of the follow up, although a primary method for survival analysis was not pre-specified in the protocol. The analysis showed that the median survival times in the subjects treated with Sipuleucel T and APC-Placebo were 25.9 and 21.4 months, respectively, a difference of 4.5 months. This difference reached statistical significance ($p = 0.010$) by log rank test. The unadjusted HR was 1.71 [95% confidence interval (CI): 1.13, 2.58]. Therefore, study D9901 failed in achieving its primary objective, but a *post hoc* analysis demonstrated an apparent survival increase in sipuleucel T-treated subjects, the basis for the efficacy claim in this BLA submission.

Possible confounders of Survival: There were a number of baseline imbalances in disease characteristics noted between study arms. Specifically there were more patients with bone only disease in the treatment arm (42% vs. 24%) and more patients with soft tissue disease in the placebo arm (71% vs. 57%). Sensitivity analyses described in the statistical reviewer's AC briefing document adjusting for single baseline covariate effects did not demonstrate confounding, but several analyses adjusting for multiple covariates including: one that incorporated Localization of disease, Gleason Score (≤ 6, 7, ≥ 8), PSA (<20, 20 - <100, ≥ 100) resulted in p values > 0.05 (Table 1, statistical reviewer's AC briefing document).

Concomitant medications: Non-steroidal antiandrogen (e.g., flutamide, nilutamide or bicalutamide) use was not reported during the study however 2 patients received chemotherapy during the study. Nineteen (23%) of patients on the sipuleucel T group vs. 4 (9%) of patients on the placebo group received corticosteroids. Ketoconazole use was reported by the sponsor in only 4 patients on the active arm; however review of CRF's revealed 3 additional patients on the active arm and 4 additional patients on the placebo arm who were receiving ketoconazole.

Subsequent chemotherapy: Chemotherapy subsequent to progression could potentially have confounded chemo effects however more patients received chemotherapy on the placebo arm compared with the sipuleucel T arm. An analysis of survival data in D9901 comparing patients who received chemotherapy following progression versus other patients showed that those who received chemotherapy had better survivals, however after removal of patients who received docetaxel the p value of the survival results was still <0.05, suggesting that subsequent therapy with docetaxel did not confound the survival results.

D9902A: The D9902A trial was originally designed to be a companion trial to D9901: eligibility, endpoints, treatment plan, monitoring, accrual goals and statistical analysis plans were initially the same in both studies. Study D9902A was terminated early because of the overall negative findings from D9901. Ninety-eight patients were enrolled out of a planned 120 patients: 65 were randomized to receive sipuleucel T and 33 to APC-Placebo. As a result of this early termination, D9902A was underpowered to reach its primary objective of improved time to progression. The estimated median time to disease progression in D9902A was 10.9 weeks in the sipuleucel T arm compared with 9.9

weeks in the APC- Placebo arm (p=0.72); median survival times were 19.0 months and 15.7 months, respectively (p = 0.331, log rank test). Efficacy results for the two trials are summarized below. Please note that there is an overlap in the 95% CI of the median survivals in the two treatment arms of study 9901:

Table 1: Combined Summary of Efficacy, D9901 and D9902A

Study	Median TTP (weeks)		Median Survival (months) (95% CI)	
	Sipuleucel-T	APC Placebo	Sipuleucel-T	APC Placebo
D9901	11.0	9.1 (p = 0.085)	25.9 **(20.0, 32.4)**	21.4 **(12.3, 25.8)** (p = 0.01)
D9902A	10.9	9.9 (p = 0.72)	19.0	15.7 (p = 0.33)

Conclusions regarding treatment effect on survival: Most sensitivity analyses supported the finding of a survival difference between study treatment arms, and the findings of 9902A, although underpowered, at least were in the same direction. The 4.5 month estimated difference in median survivals between treatment arms greatly exceeds the known 2.5 month survival benefit reported in the docetaxel study in a similar population, and is therefore of unquestioned clinical benefit. However, questions remain regarding the persuasiveness of these survival findings. There were many baseline imbalances and although most sensitivity analyses supported the survival advantage, there were some sensitivity analyses that did not.

Safety results: The safety database was mainly derived from 147 patients who received sipuleucel T and 78 patients who received APC-placebo; a total of 225 subjects in trials D9901and D9902A. Since these studies were similar in design and eligibility, safety results were pooled from the two studies. More than 88% of the subjects received the scheduled 3 infusions of either sipuleucel T or APC-Placebo. Overall, sipuleucel T treatment was relatively well tolerated. Most sipuleucel T treated patients developed Adverse Events (AEs), but most of these were grade 1 to 2 and resolved within 48 hours. Chills, fatigue pyrexia, and back pain were the most common AE's (> 25% of subjects who received sipuleucel T). These events generally occurred within 1 day of an infusion with sipuleucel T, were Grade 1 or 2, were managed on an outpatient basis, and had median durations of 24 to 48 hours. No deaths were reported to be related to the infusion of sipuleucel T and no deaths occurred within 30 days after the infusion. Twenty-four percent (23.8%) of sipuleucel T treated subjects developed Serious Adverse Events (SAEs) other than death, not different from 23% of APC-Placebo treated subjects. These SAEs included life-threatening adverse events, inpatient hospitalization or prolongation of existing hospitalization, or a persistent or significant disability/incapacity. However, 5.4% (8 out of 147) sipuleucel T treated subjects experienced CVA-related SAEs, compared to none in APC-Placebo treated subjects in D9901 and D9902A. The sponsor subsequently submitted summarized results for CVA events observed in all the phase 3 trials, including p-11 in androgen dependent prostate cancer and D9901, D9902A and ongoing study D9902B in the proposed indication. Eighteen out of 461 (3.9%) subjects treated with sipuleucel T developed CVA events compared to 6 out of 231 (2.6%) in the APC-Placebo treated subjects, an absolute increase of 1.3% (odds ratio = 1.5). Two percent (7/345) of subjects in the sipuleucel T arm died from CVA events compared to 1.2 % of subjects in the APC- Placebo arm (2/172), an absolute increase of 0.8%. In the proposed indication, approximately three times as many subjects experienced CVA's in the treatment group compared with controls. Although these differences did not reach statistical significance, the increased CVA frequency in sipuleucel T treated subjects is a potential safety concern.

FDA Advisory Committee meeting: On March 29, 2007, FDA held an advisory committee meeting of the Cellular, Tissue and Gene Therapies Advisory Committee, supplemented by members of the Oncology Drugs Advisory Committee and several prostate cancer specialists, to seek advice on the persuasiveness of submitted sipuleucel T efficacy and safety results. Several questions regarding product potency, variability and mechanism of action were also discussed. After extensive discussions regarding the significance of the CVA's reported in the 2 efficacy studies and additional studies with sipuleucel T, the committee voted unanimously (17-0) that safety had been established. The Committee recommended that post-marketing pharmacovigilance studies be performed to monitor the incidence of CVA's with attention to the African- American population and other minorities. The Committee was asked to vote whether or not submitted data established the efficacy of sipuleucel-T (APC-8015) in the intended population. The official record shows that the vote was 13 yes and 4 no in favor of evidence of efficacy. However, most of the advisory committee members expressed misgivings about the persuasiveness of the efficacy data. After two members initially voted against efficacy, the committee requested clarification, and the question was changed from 'establish efficacy' to 'substantial evidence.' The two members then changed their vote from no to yes and an additional member stated that he would have voted no to the original question but yes to the revised question. Only seven out of the 17 voting Committee members voiced an opinion that the data clearly demonstrated efficacy, and one member stated that he voted yes to "promote this type of research." The interpretation of the advisory committee vote on efficacy is therefore problematic, however, Committee members did agree that the confirmatory phase 3 study 9902B must be completed, and that the under representation of the African American population should be addressed.

Conclusions: It is difficult to quantify the persuasiveness of the survival findings, given the effects of multiplicity; therefore no p value could be applied to the survival difference. The submitted studies are very small compared with successful studies in hormone refractory prostate cancer. The statistical simulation performed using --b(4)---distributions suggests that the chance that the survival findings could be attributable to chance in such a small study population may actually be as high as 15%. As mentioned previously, there is an overlap in the 95% CI of the median survivals in the two treatment arms of study 9901. The lack of a treatment effect on tumor responses, PSA responses, delays in time to progression or delays in time to onset of pain despite the striking survival findings do not lead credence to attribution of the survival effects to the therapy. The reported study results are clearly clinically meaningful, however they do not meet the regulatory criteria for licensure as described in the guidance on Clinical Evidence of Effectiveness for Human Drug and Biological Products, which states: "In order for a single trial to support registration, the trial must be well conducted, and the results of the trial must be internally consistent, clinically meaningful, and statistically very persuasive." Statistically highly persuasive has been interpreted variously, as a one-sided $p \leq 0.0025$-0.005 but in no case has a $p > .01$ been accepted. The submitted single study results are much less persuasive, particularly since they are based on a single small trial which failed its primary endpoint. The advisory committee recommendations regarding efficacy are difficult to interpret, however committee members did agree that additional information from ongoing study 9902B will provide definitive evidence of efficacy. If Sipuleucel-T were to be licensed now on the basis of a survival advantage, it may be logistically and ethically problematic to finish the study 9902B.

Accelerated Approval: 'Accelerated approval' has been considered to be an option, du to the increased regulatory authority to require post marketing studies and to withdraw marketing approval if the studies are not performed or do not support the efficacy of the product. Under 21CFR 601.40 Subpart E : Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses: These regulations describe approval of 'certain biological products that have been studied for their safety and effectiveness in treating serious or life- threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).' In the proposed indication, available therapy is considered to be docetaxel, which is approved, in combination with prednisone for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer. (see Guidance for Industry, Available therapy, http://www.fda.gov/cber/gdlns/availther.htm) In oncology drug regulation, 'meaningful therapeutic benefit' is defined by a population that is clearly refractory to or intolerant of available therapy, which in this case would be docetaxel. Since only 8% of patients had received prior chemotherapy, this population could not be considered refractory to available therapy, and since over 50% of patients received chemotherapy following progression, the population could not be considered intolerant of chemotherapy.

In addition, 21CFR 601.41 specifies that Accelerated Approval can be "based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity," and further states that "FDA may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Since the BLA claim was based on a survival finding, approval based on a surrogate would appear to have no regulatory basis. Because CD54, a cell surface marker on dendritic cells, was a potency release criterion, all sipuleucel T subjects had CD54 expression and cell count data. Kaplan Meier survival was analyzed by 3 groups: patients who received placebo and those who received sipuleucel T whose CD54 upregulation ratio was below the median and those who received sipuleucel T whose CD54 upregulation were at or above the median. These results suggest that there may be a relationship between CD54 and some clinical effect, however since these results are again *post hoc* and could be considered responder analyses, reflecting patient prognostic factors rather than the effects of therapy, the further validation of this biomarker will await the analysis of the ongoing study 9902B. There is insufficient evidence provided in the BLA to support use of this biomarker in support of accelerated approval.

Clinical Team Leader's Recommendations: Due to uncertainties surrounding the treatment effect, I recommend waiting for additional efficacy data from 9902B: either the interim or final analysis, prior to licensure. The sponsor estimates that the interim analysis for 9902B, based on 180 events, will occur in August 2008 and the final analysis, based on 360 events, will occur around the end of 2010. An earlier interim analysis would not be recommended, since it could compromise the power of the study to detect a survival difference. Accelerated Approval is not an option, as noted above and given the survival claim.